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(71) Applicant *(for all designated States except US)*: RIJKSUNIVERSITEIT TE GRONINGEN [NL/NL]; Broerstraat 5, NL-9712 CP Groningen (NL).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : VAN DE GRAMPEL, Johan, Christoph [NL/NL]; Kamperfoelieweg 45, NL-9765 HJ Paterswolde (NL). VAN DER HUIZEN, Adriaan, Albert [NL/NL]; 1e Willemstraat 57, NL-9725 JB Groningen (NL).

(74) Agent: URBANUS, H., M.; Vereenigde Octrooibureaux, Nieuwe Parklaan 107, NL-2587 BP Den Haag (NL).

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(57) Abstract

An aziridino derivative of a tetrameric cyclochlorophosphazene compound having the formula $N_4P_4Cl_{8-n}Az_n$, in which Az represents aziridino and n = 1, 2, 3, 4, 5, 6 or 7; a process for bonding such an aziridino derivative by aminolysis in a reaction solution of a compound having the formula $N_4P_4Cl_{8-n}Az_n$, in which n = 0, 1, 2, 3, 4, 5, or 6, and recovering the resulting aziridino derivative by means of 'high performance liquid chromatography' as well as an aziridino derivative - based on the resulting aziridino derivative - of a tetrameric substituted cyclophosphazene compound having an anti-tumor acitivity and having the formula $N_4P_4R_{8-n}Az_n$, in which n = 1, 2, 3, 4, 5, 6 or 7 and R represents the same or different substituents.

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AZIDIRINO DERIVATES OF TETRAMERIC CYCLOPHOSPHAZENES

The invention relates to an aziridino derivative of a tetrameric cyclochlorophosphazene compound.

The $(NPCL_2)$-tetramer having the formula $N_4P_4Cl_8$ and the compound $N_4P_4Az_8$ derived therefrom, in which Az is aziridino, are known from the article by V.A. Chernov, V.B. Lytkina, S.I. Sergievskaya, A.A. Kropacheva, V.A. Parshina and L.E. Sventsitskaya, Farmakol. Toksikol. (Moscow) 22, 365 (1959). Of the compound $N_4P_4Az_8$ it is indicated that it has an anti-tumor activity with respect to S-45 sarcoma in rats.

Moreover, Inorg. Chem. 3 (1964) 757-761 discloses that the compound $N_4P_4Az_8$ can be prepared by complete aminolysis of the tetrameric $N_4P_4Cl_8$ by means of aziridine or a homologue thereof in an aromatic hydrocarbon as reaction medium and triethylamine as acid acceptor.

It is an object of the invention to provide an aziridino derivative of a tetrameric cyclochlorophosphazene compound which may serve as starting-material in the synthesis of tetrameric cyclophosphazene compounds to be derived therefrom and containing one or more aziridino groups by substitution of the chlorine atoms by a properly selected substituent, of which latter compounds it may be expected that they also have an anti-tumor activity.

For this purpose the invention provides a compound of the type defined in the opening paragraph, characterized by the formula $N_4P_4Cl_{8-n}Az_n$, in which n = 1,2,3,4,5,6 or 7.

Although the preparation of the compounds according to the invention proceeds rather easily with good precautions, the isolation of different, mostly isomeric products is not easy. E.g. the reaction of $(NPCL_2)_4$ with aziridine gives at a molar ratio of 1:3.5, mainly the 6 products

$N_4P_4Cl_7Az$

gem-$N_4P_4Cl_6Az_2$

1,3-cis-$N_4P_4Cl_6Az_2$

1,5-cis-$N_4P_4Cl_6Az_2$

1,3-trans-$N_4P_4Cl_6Az_2$

1,5-trans-$N_4P_4Cl_6Az_2$, in addition to a number of products $N_4P_4Cl_5Az_3$. A schematic representation of the structural formulae of these compounds, in which the ring-N-atoms and the Cl-atoms have been omitted, is given by formulae 1-6 of the sheet of formulae.

In accordance with what has been stated in the preceding paragraph the invention therefore also relates to a process for preparing an aziridino derivative according to the invention by aminolysis in a reaction solution of a cyclopolychlorophosphazene compound and working up of the reaction mixture, which process is characterized in that in a compound having the formula $N_4P_4Cl_{8-n}Az_n$, in which n = 0,1,2,3,4,5 or 6, 1-7 chlorine atoms are substituted by an aziridino group and that the resulting aziridino derivative are recovered from the product obtained after working up of the reaction mixture by means of HPLC ("high performance liquid chromatography").

In the process according to the invention the selection of column material and eluent depends, within the scope of application of the HPLC technique, on the reaction mixture to be analyzed.

As will be elucidated hereinafter, the ratio of mono-aziridino to polyaziridino substitution is, e.g. in the case of starting from $(NPCL_2)_4$, the ratio in the reaction product of mono-aziridino to di-aziridino substitution, to be varied by affecting the molar ratio of the reaction components and, if required, the reaction time.

A suitable solvent in which the process according to the invention can be carried out is dry diethyl ether, but also benzene, pentane, hexane and THF (tetrahydrofuran) are suitable for having reactions carried out therein.

The aziridinc derivative of the tetrameric cyclochlorophosphazene compounds according to the invention are suitable starting materials for preparing compounds therefrom, the chlorine atoms being replaced by properly selected other substituents. In view of the teaching from later published Dutch patent application no. 83.00573 it may be expected that such compounds have an anti-tumor activity.

Consequently, the invention also relates to an aziridino derivative of a tetrameric substituted cyclophosphazene compound having an anti-tumor activity, characterized by the formula $N_4P_4R_{8-n}Az_n$, in which n = 1,2,3,4,5,6 or 7 and R represents the same or different substituents.

Preferably, R is an electron donating group of low sensitivity to hydrolysis.

The invention will be illustrated by the example given herein below.

Example I

Preparation of $N_4P_4Az_nCl_{8-n}$ (n=1,2).

$(NPCL_2)_4$ (Otsuka Chem.) was recrystallized from hexane before use. Aziridine was distilled from KOH pills under dry nitrogen just before use. Solvents were purified and dried in the conventional manner. Reactions were carried out under a dry nitrogen atmosphere. ^{31}P and ^{1}H NMR spectra were measured with a Nicolet 283A FT spectrometer equipped with an NTCFT-1180 data system, in 10 mm tubes at 25°C. The deuterium resonance of the solvent ($CDCl_3$) was used as "field-frequency lock". HPLC separations were carried out by using two Waters 6000A liquid pumps (each having a capacity of 20 cm^3/min.) and a Waters R401 refractometer. Lichrosorb Si 60/10 served as column material.

A. Reaction of $(NPCL_2)_4$ with aziridine in the molar ratio of 1:2.5.

A solution of 1.4 cm^3 of aziridine (27.1 mmol) in 150 cm^3 of dry diethyl etherwas added dropwise to a solution of 5.0 g of $(NPCl_2)_4$ (10,8 mmol) in 300 cm^3 of dry diethyl ether for 30-45 min., while vigorously stirring and cooling to - 20°C. After the reaction mixture was warmed up slowly to room temperature and after a reaction time of 18 hours filtration of the polymeric amino-HCL salt and evaporation of the filtrate gave 5.1 g of a white waxy oil which turned out to be slightly sensitive to hydrolysis (Product A).

B. Reaction of $(NPCL_2)_4$ with aziridine in the molar ratio of 1:3.5.

A solution of 3.9 cm^3 of aziridine (77.8 mmol) in 100 cm^3 of dry diethyl ether was added dropwise to a solution of 10.0 g $(NPCl_2)_4$ (21.6 mmol) in 400 cm^3 of dry diethyl ether for 30-45 min., while vigorously stirring and cooling to - 0°C. The reaction mixture

was warmed up slowly to room temperature and stirred further until a total reaction time of 7 hours. The working up procedure as set forth below A. gave 10.5 g of a turbid oil sensitive to hydrolysis (Product B).

C. Analysis of the products.

Analysis of ^{31}P NMR and mass spectra as well as HPLC diagrams (Fig. 1 and Fig. 2) showed that products A and B had the same composition in principle. A especially contained $N_4P_4AzCl_7$ while B, in addition to this component, especially contained $N_4P_4Az_2Cl_6$ (namely 5 isomers). The ratio of mono/disubstitution was to be affected by varying the molar ratio and the reaction time. It turned out that a reaction mixture such as product B was also to be obtained starting from $N_4P_4AzCl_7$, in a 1:2 reaction with aziridine in dry diethyl ether.

D. Separation methods

It turned out that both product A and product B could be separated with HPLC by using a 25% diethyl ether/75% hexane eluent. Product A gives $N_4P_4AzCl_7$ as the largest fraction (Fig 1, fraction 1). In total, 2.56 g were obtained (yield 50%). Recrystallization from pentane gave 1.9 g of analytically pure material; melting point 68.5-70.0°C.

Under corresponding conditions product B gave seven fractions (Fig. 2):

Fraction no.:	(1) $N_4P_4AzCl_7$	1.54 g	
	(2) $N_4P_4Az_2Cl_6$	2.12 g	} different isomers
	(3) "	1,26 g	
	(4) "	0,65 g	
	(5) $N_4P_4Az_2Cl_6$	1.63 g	

Fraction no.: (6) $N_4P_4Az_3Cl_5$ 0.57 g } different isomers
(7) $N_4P_4Az_3Cl_5$ 0.38 g }
Total 8.15 g = 77.8% on product B.

It turned out that fraction 5 consisted of 2 components which were once again separated afterwards with the same eluent (Fig. 3).

Yield.

Fraction no.: 5^{I} : $N_4P_4Az_2Cl_6$ 0.20 g
5^{II} : $N_4P_4Az_2Cl_6$ 1.02 g
Total 1.22 g = 75%, calculated on fraction 5 (1.63 g).

E. Characterization

Mass spectra

The mass spectra of both $N_4P_4AzCl_7$ and $N_4P_4Az_2Cl_6$ showed different chlorine isotope peaks in addition to parent peaks of respectively M^+ = 467 (for ^{35}Cl) and M^+= 474 (for ^{35}Cl). The spectra of the different isomeric forms of $N_4P_4Az_2Cl_6$ were not distinguishable.

Infrared spectra

$N_4P_4AzCl_7$ gave a ring frequency at 1316 (broad) or 1279 cm^{-1} (sharp); the "aziridino" band lay at 965 cm^{-1} (sharp). The IR spectra of the isomeric compounds $N_4P_4Az_2Cl_6$ were clearly distinguishable. Ring frequencies varied from 1310-1334 cm^{-1} (broad) or from 1275-1279 cm^{-1} (sharp). Aziridino bands were visible from 963 to 976 cm^{-1} (sharp).

NMR spectra

	Substance	HPLC fraction	^{31}P spectrum (form)	δP_A	δP_M	δP_X	$^2J_{AM}$ (Hz)	$^2J_{MX}$ (Hz)	δ^1H	$^3J_{PH}$ (Hz)	Isomer
5	$N_4P_4AzCl_7$	1	AM_2X	8.57	-4.68	-7.17	27.6	30.6	2.35	22	
	$N_4P_4Az_2Cl_6$	2	A_2X_2	8.37		-1.92	27.9		2.32	22	(1,5)
	$N_4P_4Az_2Cl_6$	3	A_2X_2	8.71		-2.61	28.4		2.32	22	(1,5)
	$N_4P_4Az_2Cl_6$	4	AA'XX'	11.88		-4.67			2.30	22	(1,3)
	$N_4P_4Az_2Cl_6$	5^{II}	AA'XX'	10.38		-4.85			2.29	22	(1,3)
10	$N_4P_4Az_2Cl_6$	5^{I}	AM_2X	18.80	-6,2(multiplet)				2.26	16.5	gem.

^{31}P "chemical shifts" in ppm relative to H_3PO_4 85%; ^1H "chemical shifts" in ppm with TMS as reference.

Elemental analysis and melting points

HPLC-fraction	Substance	mpt.(°C)	C(%)	H(%)	N(%)	P(%)	Cl(%)
1	$N_4P_4AzCl_7$	68,5- 70	5,07(5.11)	0,84(0,86)	14,85(14,90)	26,31(26,35)	52,60(52,78)
2	$N_4P_4Az_2Cl_6$	103 -104	10,11(10,08)	1,60(1,69)	17,56(17,63)	26,17(25,99)	44,63(44,62)
3	$N_4P_4Az_2Cl_6$	122,5-123,5	10,08(10,08)	1,61(1,69)	17,66(17,63)	25,84(25,99)	44,64(44,62)
4	$N_4P_4Az_2Cl_6$	91 - 92	10,21(10,08)	1,68(1,69)	17,73(17,63)	25,98(25,99)	44,29(44,62)
5^{II}	$N_4P_4Az_2Cl_6$	74 - 75	10,43(10,08)	1,66(1,69)	17,47(17,63)	25,92(25,99)	44,53(44,62)
5^{I}	$N_4P_4Az_2Cl_6$						

Fraction 0 is solvent.

The calculated values are mentioned in brackets.

$N_4P_4AzCl_7$ was recrystallized from pentane; all the other substances mentioned above, apart from fraction 5^{I}, were crystallized from a mixture of diethyl ether and pentane.

Example II

Preparation of a number of aziridino derivative having the formula $N_4P_4R_{8-n}Az_n$.

In de preparation of the abovementioned aziridino derivative the resulting reaction mixture was worked up according to procedure (a) mentioned herein below:

Procedure (a)

Most reactions afforded considerable amounts of hydrochloride salts, either precipitated or in solution. The use of aziridine as a hydrochloride scavenger resulted in the aziridino chloride salt which is rather unstable and subsequently polymerized.

Precipitated (polymeric) salts are removed by filtration and, after washing thoroughly with solvent, the combined filtrates containing the P-N ring compounds are evaporated in vacuo. If acetonitrile or THF is used as solvent, the complete reaction mixture is evaporated in vacuo. Extraction with diethyl ether or benzene yields solutions of the salt-free crude products.

All crude products are purified by recrystallization from an appropriate solvent. Mixtures are separated by HPLC and the resulting fractions are subsequently recrystallized.

Preparation of $N_4P_4AzAm_7$ and $N_4P_4Az_2Am_6$ (Am = NHme, NMe_2, wherein me = methyl: compounds nos. 11-22): the compounds having formulae 1-5^{II} of the sheet of formulae were used as starting compounds.

$N_4P_4Az(NHMe)_7$ and $N_4P_4Az_2(NHMe)_6$.

To a stirred solution of 0,5 g (ca. 1 mmol) of the ring compounds in 15 cm^3 of chloroform, cooled at 0°C, were slowly added 15cm^3 of a 1 M solution of methylamine in benzene. After warming up to room temperature and a reaction time of 18 h application of procedure (a) afforded the crude products. There was obtained a white solid when the compound having formula 2 of the sheet of formulae was used as starting compound. In all other cases the products consisted of resinous oils. All compounds were recrystallized several times from mixtures of diethyl ether and methylene chloride. When the compound having formula 5^{II} of the sheet of formulae was used as starting material, a contaminated oil was obtained. Mass and NMR spectra indicated the presence of the completely aminolyzed product. Further data are listed in Table I given herein below.

TABLE I

Data on the preparation of compounds nos.11-16

Starting compounds (formula-no. of sheet of formulae)	Product (compound no.)			Yield (%)	mmpt(°C)
1		$N_4P_4Az(NHMe)_7$	11	36	96-98
2	1_1 trans-5	$N_4P_4Az_2(NHMe)_6$	12	56	124-126
3	1_1 cis-5	$N_4P_4Az_2(NHMe)_6$	13	52	135-137
5^I	gem.	$N_4P_4Az_2(NHMe)_6$	14	75	136-138
4	1_1 trans-3	$N_4P_4Az_2(NHMe)_6$	15	19	104-106.5
5^{II}	1_1 cis-3	$N_4P_4Az_2(NHMe)_6$	16	75[a]	-

a - resinous oil

$N_4P_4Az(NMe_2)_7$ and $N_4P_4Az_2(NMe_2)_6$

To a stirred solution of 0.5 g (ca. 1 mmol) of the ring compound in 25 cm^3 diethyl ether, cooled at 0°C, was added dropwise 15 cm^3 of a 3 M dimethylamine solution in diethyl ether. After warming up to room temperature and a reaction time of 18 h, the working up by using procedure (a) yielded 0.57 g of an oily material. This was dissolved in 25 cm^3 of diethyl ether and refluxed overnight after adding 10 cm^3 of a 3 M dimethylamine solution in diethyl ether. Subsequently, procedure (a) was once again used, yielding 0.54 g of a white solid (if the starting material is the compound having formula 1 or formula 2 of the sheet of formulae) or a viscous oil (if the starting material is the compound having formula 3 or formula 5^{II} of the sheet of formulae). The solid was easily crystallized from hexane, whereas the oil required several recrystallizations from small amounts of hexane at -70°C. The product obtained by starting from the compound having formula 2 of the sheet of formulae remained an oil of unsatisfactory purity. Mass and NMR spectra were in agreement with the completely aminolyzed compound no. 22. Further data are listed in table II given hereinbelow.

TABLE II

Data on the preparation of compounds nos. 17-22

Starting compounds (formula-no. of sheet of formulae)	Product (compound no.)			Yield (%)	m.p.(°C)
1		$N_4P_4Az(NMe_2)_7$	17	34	206-208
2	1_1 trans-5	$N_4P_4Az_2(NMe_2)_6$	18	68	198-200
3	1_1 cis-5	$N_4P_4Az_2(NMe_2)_6$	19	32	192-195
5^I	gem.	$N_4P_4Az_2(NMe_2)_6$	20	33	dec. >200
4	1_1 trans-3	$N_4P_4Az_2(NMe_2)_6$	21	24	dec. >200
5^{II}	1_1 cis-3	$N_4P_4Az_2(NMe_2)_6$	22	100[a]	-

a - oily material

Characterization data

TABLE III

^{31}P NMR data[a] of the compounds nos. 6 - 22

Compound no.	$\delta^{31}P$(ppm) δP(1)	δP(3)	δP(5)	δP(7)	$^2J_{PP}$(Hz) J_{13}	J_{35}	J_{57}	J_{17}	$^4J_{PP}$ (Hz)
6	18,5	-3,4	6,9	-3,4	13,9	26,4	26,4	13,9	
7	12,1	14,9	12,1	-2,5	27,0	27,0	26,5	26,5	
8	10,3	13,7	11,7	-1,8	28,9	27,6	24,7	26,9	
9	19,6	11,3	-4,4	-6,8	22,8	25,6	27,9	12,0	
10	10,3	12,2	10,3	-3,5	29,4	29,4	27,8	27,8	
11	13,8	9,6	9,7	9,6	32,6	44,6	44,6	32,6	
12	13,6	9,5	13,6	9,5	32,3	32,3	32,3	32,3	
13	13,9	9,6	13,9	9,6	32,9	32,9	32,9	32,9	
14	19,1	9,5	9,4	9,5	30,5	42,7	42,7	30,5	
15	13,8	13,8	9,6	9,6	27,2	33,0	39,8	33,0	0
16	13,5	13,5	9,5	9,5	27,2	33,1	39,5	33,1	-0,2
17	13,3	9,6	8,6	9,6	36,2	49,2	49,2	36,2	
18	12,8	9,6	12,8	9,6	38,3	38,3	38,3	38,3	
19	13,9	9,6	13,9	9,6	39,8	39,8	39,8	39,8	
20	19,2	10,3	8,5	10,3	29,5	41,4	41,4	29,5	
21	14,0	14,0	8,6	8,6	31,7	38,9	43,6	38,9	-0,4
22	12,5	12,5	8,3	8,3	33,0	39,9	43,5	39,9	-0,1

a- "Chemical Shifts" relative to 85 % H_3PO_4

TABLE IV

Elemental analysis data[a] of compounds Nos. 6 - 22

Compound No.	C(%)	H(%)	N(%)	Cl(%)
6	14,95(14,91)	2,49(2,50)	20,35(20,28)	36,86(36,67)
7	14,75(14,91)	2,43(2,50)	20,36(20,28)	36,44(36,67)
8	14,72(14,91)	2,57(2,50)	20,41(20,28)	36,96(36,67)
9	14,89(14,91)	2,51(2,50)	20,37(20,28)	36,72(36,67)
10	-	-	-	-
11	24,87(25,00)	7,46(7,46)	38,35(38,88)	
12	26,90(27,03)	7,26(7,26)	37,43(37,83)	
13	26,94(27,03)	7,37(7,26)	37,79(37,83)	
14	27,24(27,03)	7,31(7,26)	36,89(37,83)	
15	26,92(27,03)	7,32(7,26)	37,12(37,83)	
17	36,34(36,22)	8,78(8,74)	31,64(31,68)	
18	36,35(36,36)	8,36(8,39)	31,43(31,80)	
19	36,48(36,36)	8,41(8,39)	32,25(31,80)	
20	36,23(36,36)	8,35(8,39)	31,20(31,80)	
21	36,53(36,36)	8,61(8,39)	32,21(31,80)	

a - the calculated values are mentioned in brackets

"In vitro" physiological activity

Compound no.	LAD (µm)	ID_{50} (µm)
11	150	56,9
12	0.6	4,6
13	0.6	4,6
14	18	6,5
15	2,5	1,8
16	-	- (not tested)
17	62	12,0
18	1,0	7,5
19	4	5,5
20	2	running test
21	2	" "
22	-	- (not tested)

Compounds nos. 12 and 18 are now measured "in vivo": LD_{50}-values are compound no. 12 : 165 mg/kg; 18 : 200 mg/kg (mice). Testing compound no. 12 for L 1210 leukemia in mice gives the following picture.

Doses:		T/C (= "Treated /Control") %
	100 mg/kg	$\geqslant$ 300 (3 mice out of 5 alive)
	120 mg/kg	T/C 225
	140 mg/kg	T/C 225 (one mouse alive)
	160 mg/kg	T/C 250 (2 mice alive)

(tests conducted with mice taken in groups of 5).

CLAIMS

1. An aziridino derivative of a tetrameric cyclochlorophosphazene compound, characterized by the formula $N_4P_4Cl_{8-n}Az_n$, in which n = 1,2,3,4,5,6 or 7.

2. A process for preparing an aziridino derivative according to claim 1, by aminolysis in a reaction solution of a cyclopolychlorophosphazene compound and working up the reaction mixture, characterized in that in a compound having the formula $N_4P_4Cl_{8-n}Az_n$, in which n = 0,1,2,3,4,5 or 6, 1-7 chlorine atoms are substituted by an aziridino group and from the product obtained after working up of the reaction mixture the resulting aziridino derivatives are recovered by means of HPLC ("high performance liquid chromatography").

3. A process according to claim 2, characterized in that the number of chlorine atoms to be substituted is varied by selection of the molar ratio of $N_4P_4Cl_{8-n}Az_n$ to aziridine, optionally in combination with the reaction time.

4. An aziridino derivative of a tetrameric substituted cyclophosphazene compound having an anti-tumor activity, characterized by the formula $N_4P_4R_{8-n}Az_n$, in which n = 1,2,3,4,5,6 or 7 and R represents the same or different substituents.

5. An aziridino derivative according to claim 4, characterized in that R is an electron donating group of low sensitivity to hydrolysis.

6. An aziridino derivative according to claim 5, characterized by the formula $N_4P_4Az_2(NHMe)_6$.

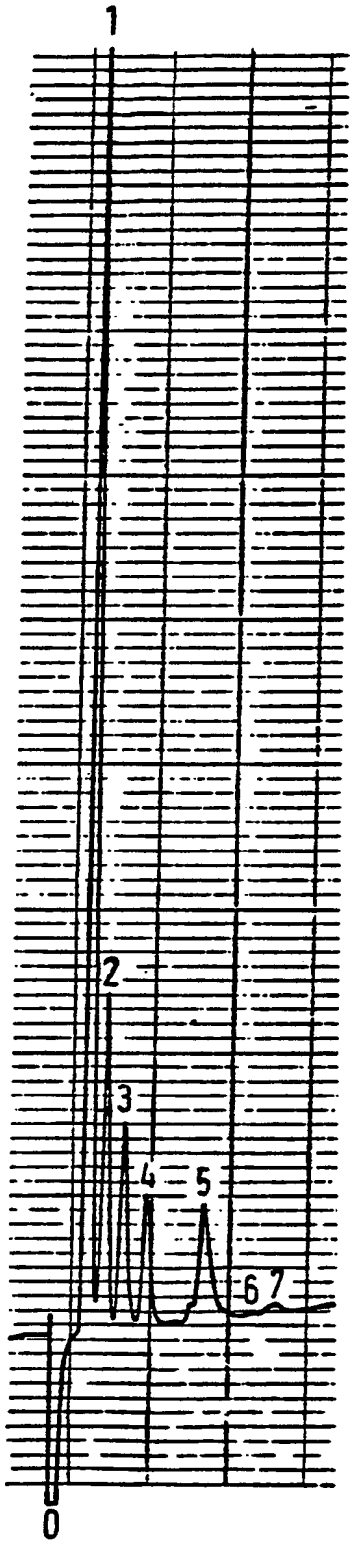


FIG.1

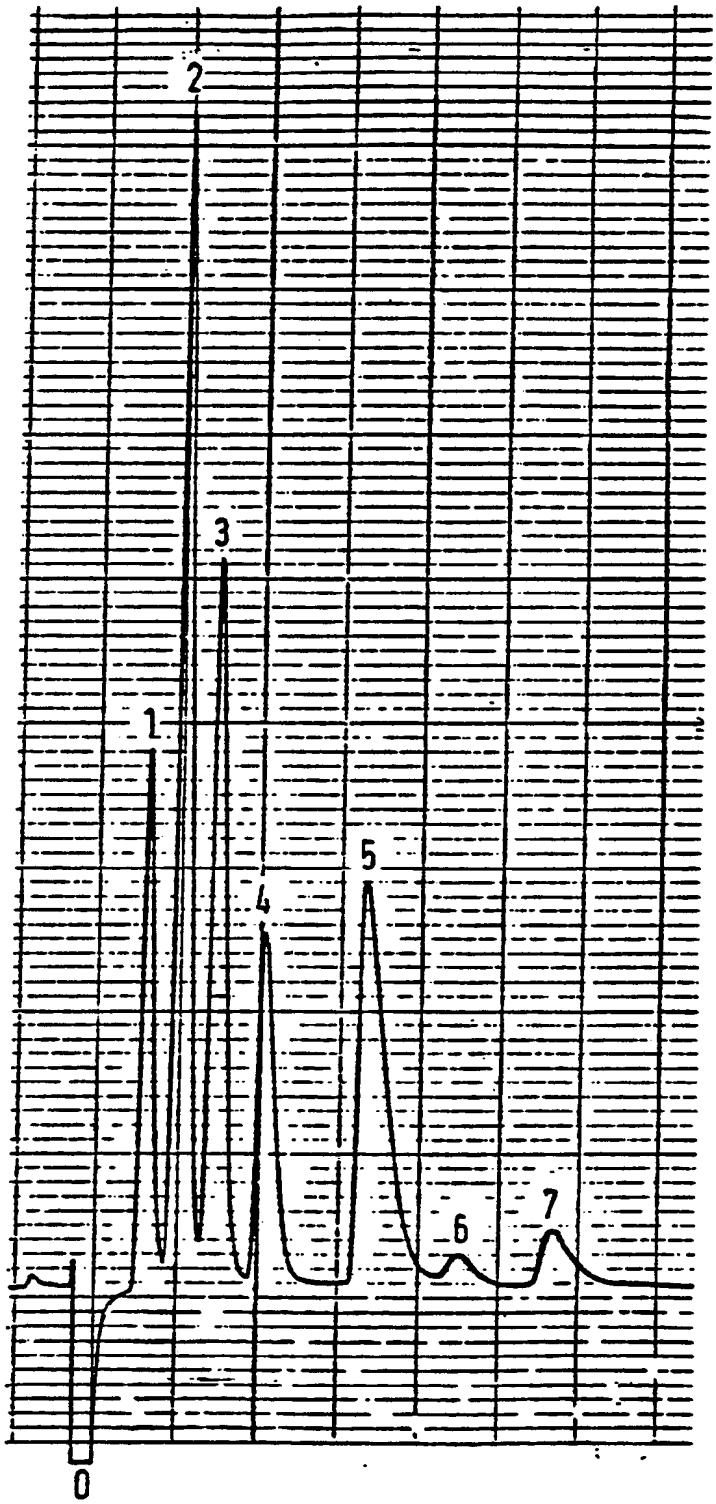


FIG.2

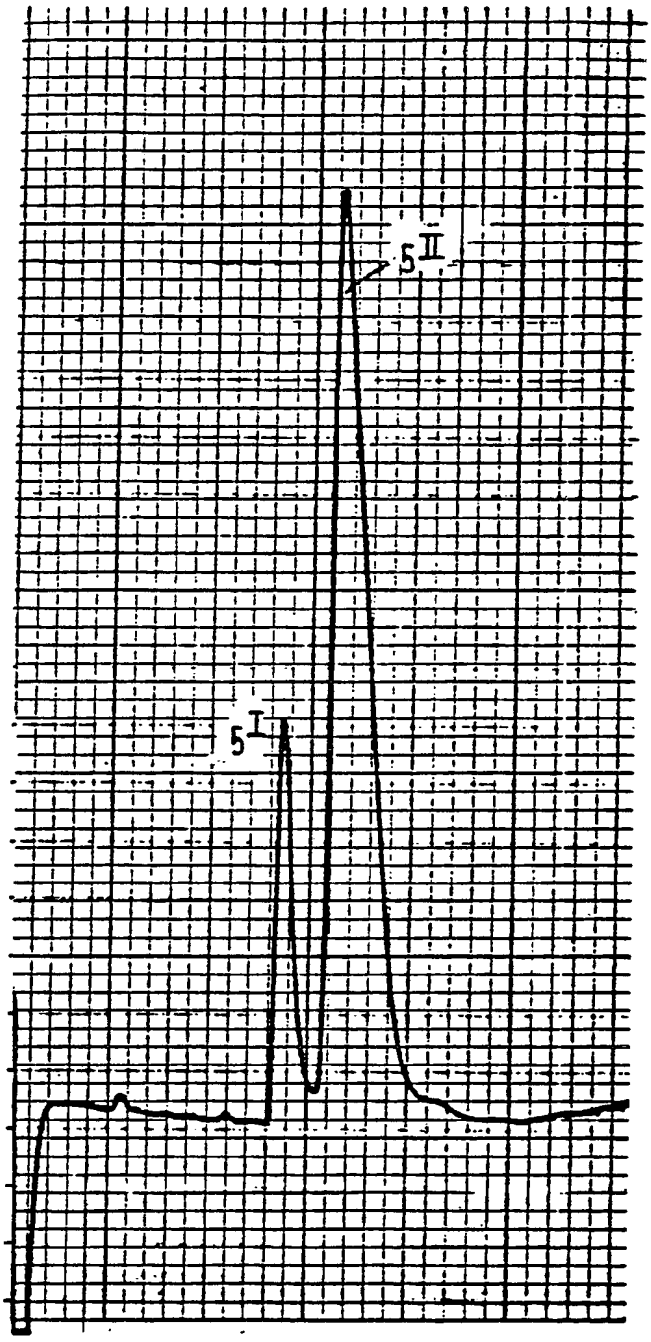
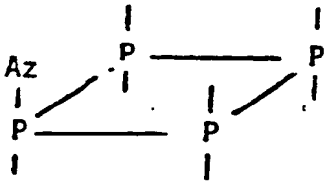


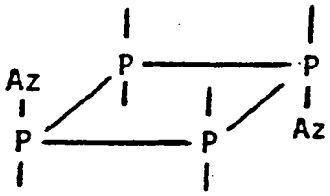
FIG.3

1

$N_4P_4Cl_7Az$:

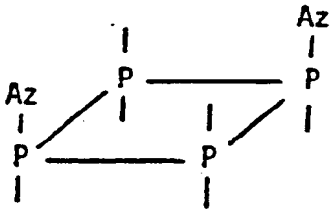


2



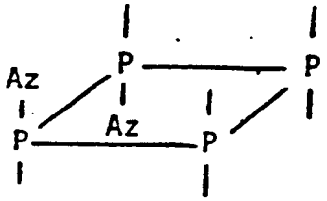
1,5-*trans*-

3



1,5-*cis*-

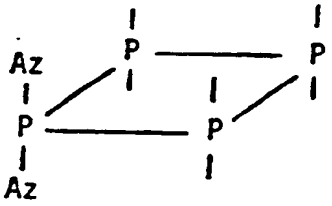
4



1,3-*trans*-

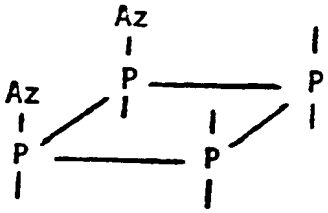
5 I

$N_4P_4Cl_6Az_2$:



gem

5 II



1,3-*cis*-

INTERNATIONAL SEARCH REPORT

International Application No PCT/NL 84/00013

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[3]: C 07 F 9/65; A 61 K 31/675

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC[3]	C 07 F 9/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
A	Chemical Abstracts, volume 54, no. 8, 25 April 1960 (Columbus, Ohio, US) V.A. Chernov et al.: "Antitumor activity of some phosphonitrile trimer and tetramer derivatives", see column 7900-i, 7901a,b,c, Farmakol. i. Toksikol. 22, 365-7 (1959) cited in the application	1-6
A	Inorganic Chemistry, volume 3, no. 5, 28 April 1964 (Easton, Pennsylvania, US) R. Rätz et al.: "Syntheses and reactions of 2,2,4,4,6,6 -Hexakis(1-aziridinyl)-cyclotriphosphaza-1,3,5-triene and related compounds", see pages 757-761 cited in the application	1-6
A	FR, A, 1493736 (SOCIETE D'ETUDES CHIMIQUES POUR L'INDUSTRIE ET L'AGRICULTRE) 1 September 1967, see the entire document	1-6

./.

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
27th July 1984	04 SEP 1984
International Searching Authority [1]	**Signature of Authorized Officer [20]**
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

Form PCT/ISA/210 (second sheet) (October 1981)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, 16 with indication, where appropriate, of the relevant passages 17	Relevant to Claim No 18
A	European Journal of Cancer, volume 15, Pergamon Press Ltd., 1979 (Oxford, GB) J.F. Labarre et al.: "Antitumor activity of some cyclophosphazenes", see pages 637-643	1-6

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/NL 84/00013 (SA 7152)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 24/08/84

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A- 1493736		None	

For more details about this annex :
see Official Journal of the European Patent Office, No. 12/82